OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

MAR 13 2002

MEMORANDUM FOR EXECUTIVE SECRETARY, ARMED FORCES EPIDEMIOLOGICAL BOARD

SUBJECT: Therapeutics Against Biowarfare Agents

The Armed Forces Epidemiological Board (AFEB) annually provides recommendations to the DoD Executive Agent on vaccines and immunization protocols necessary to enhance protection against validated biological warfare threat agents. In August of 2000, the AFEB provided the Department with a list of recommended antibiotics against biowarfare agents, as requested by the Office of the Assistant Secretary of Defense for Health Affairs. Although approved for use by the Food and Drug Administration, many of the recommended antibiotics were not labeled for the specific use recommended by the AFEB.

In this regard, I would like the AFEB to review existing Joint Operational Requirement Documents, progress on specific efforts to obtain new indications for existing therapeutics, and acquisition status of biologics (treatment and prophylaxis) against the current prioritized list of biowarfare agents and make recommendations to this office on the current status of requirements and suggested priorities. As part of the AFEB deliberations, I would expect the Board to receive briefings from the Joint Staff (Joint Service Integration Group) on existing joint requirements and the Joint Program Office on acquisition status and efforts to obtain new indications for existing therapeutics.

I request that the Board address this issue at the May AFEB meeting in concert with the periodic review of the threat list.

Ellen P. Embrey
Deputy Assistant Secretary of Defense
(Force Health Protection and Readiness)

Attachments
As stated

DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258

AFEB (15-1a) 00-9

03 August 2000

MEMORANDUM FOR THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)
THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Antibiotics Against Biowarfare Agents

1. On March 13, 2000 the Deputy Assistant Secretary of Defense for Health Operations Policy requested that the Armed Forces Epidemiological Board, in consultation with the Centers for Disease Control and Prevention (CDC), provide recommendations on the most appropriate FDA approved antibiotics to be used for treatment of the primary bacterial and rickettsial agents on the biowarfare threat list. Specifically, recommendations were requested for treatment of the organisms which cause anthrax, plague, tularemia, brucellosis, glanders, and Q fever.

2. The selection of antibiotics to prevent and treat illness from biowarfare agents has received considerable recent attention. In December 1999, a Medical Biological Defense Material (MBDM) policy meeting was held at Fort Detrick, Maryland to develop a list of preferred antibiotics for post-exposure prophylaxis. A triservice field manual "Treatment of Biological Warfare Agent Casualties," which includes antibiotic recommendations, has recently been finalized. CDC is developing a civilian pharmaceutical stockpile for prevention and treatment of illness due to large-scale bioterrorism and has also addressed the issue. Beginning in 1999, the Journal of the American Medical Association (JAMA) has begun publishing a series of articles on biological warfare agents, including treatment and prophylaxis, based on the recommendations of a Working Group on Civilian Biodefense constituted by The Johns Hopkins School of Public Health. During the May 2000 AFEB meeting, the Board heard a presentation on this topic by LtCol George Christopher from the US Army Medical Institute of Infectious Diseases, who led the effort to develop the triservice field manual, and discussed the issues with the Board and the Disease Control Subcommittee.

3. In developing the list of recommended agents, the Board reviewed the above materials and considered the following issues:

- Efficacy of the drugs against the threat agents based on peer-reviewed publications and other data sources
- Potential for antimicrobial resistance (natural and bioengineered)
- Side effects profiles of the alternative antimicrobial agents
- Ease of administration (especially dosing frequency)
- Broadness of spectrum (how many agents would be covered)
- Interactions with other drugs or products which may be used simultaneously
- Cost (including potential changes in cost as patents lapse)
- Shelf life

4. Two additional issues were also considered. Although the major group in which these drugs would be used is front-line active duty personnel, there may also be dependents (including pregnant women and children) in some high-risk settings in whom the recommended therapies are contraindicated. And while all of the therapeutics discussed is FDA licensed, they are often not labeled for the prophylaxis and treatment of biowarfare agents. Such off-label use will require that potential recipients provide informed consent to be given the medication under an established protocol. However, the Board felt that labeling status should not be the determining factor if there was a clear best option based on the other criteria.

5. The Board made the following comments and recommendations:

a. **FOR THESE SIX THREAT AGENTS, ANTIBIOTIC ALTERNATIVES ARE LIMITED FOR BOTH PROPHYLAXIS AND TREATMENT. THE MAJOR ANTIBIOTICS UNDER CONSIDERATION BASED ON BROADNESS OF SPECTRUM AND EFFICACY ARE THE FLUOROQUINOLONES (SPECIFICALLY CIPROFLOXACIN) AND TETRACYCLINES (SPECIFICALLY DOXYCYCLINE). WHEN SUBJECT MATTER EXPERTS CONSIDERED THE CRITERIA ABOVE, THERE WAS LITTLE TO DIFFERENTIATE THESE TWO CLASSES IN TERMS OF A CLEAR BEST ALTERNATIVE. DOXYCYCLINE APPEARS TO HAVE A BROADER SPECTRUM, IN THAT IT IS CONSIDERED AN ALTERNATIVE FOR ALL SIX THREAT AGENTS, AND IS CONSIDERABLY LESS EXPENSIVE THAN ANY OF THE FLUOROQUINOLONES. HOWEVER, IT WAS CONSIDERED TO HAVE A GREATER INCIDENCE OF SIDE EFFECTS, AND WAS CONSIDERED MORE HARMFUL IN PREGNANT WOMEN AND CHILDREN. THESE DRUGS WERE FELT TO BE ROUGHLY EQUIVALENT WITH RESPECT TO THE OTHER CRITERIA (SHELF LIFE, EASE OF ADMINISTRATION, POTENTIAL FOR RESISTANCE, AND DRUG INTERACTIONS). REGARDLESS OF WHICH DRUG IS SELECTED AS THE FIRST CHOICE FOR ANY OF THESE DISEASES, THE OTHER MUST ALSO BE AVAILABLE AS A BACK-UP.**

b. **THE MDBM POLICY GROUP (WHICH ADDRESSED <u>ONLY POST-EXPOSURE PROPHYLAXIS</u>) SELECTED CIPROFLOXACIN AS THE DRUG OF CHOICE FOR ANTHRAX AND TULAREMIA WITH DOXYCYCLINE AS THE BACKUP, WHILE DOXYCYCLINE WAS THE FIRST CHOICE FOR PLAGUE WITH CIPROFLOXACIN AS THE BACKUP. DOXYCYCLINE (COMBINED WITH RIFAMPICIN FOR BRUCELLOSIS) WAS CONSIDERED THE FIRST LINE PROPHYLACTIC AGENT FOR GLANDERS, BRUCELLOSIS, AND Q FEVER. THE BOARD SUPPORTS THESE CHOICES.**

c. **FOR THERAPY, CIPROFLOXACIN IS ALSO THE DRUG OF CHOICE FOR ANTHRAX WITH DOXYCYCLINE AS THE BACKUP. FOR BOTH PLAGUE AND TULAREMIA, STREPTOMYCIN IS CONSIDERED THE TRADITIONAL THERAPEUTIC DRUG OF CHOICE, BUT BECAUSE OF THE ROUTE (INTRAMUSCULAR) AND FREQUENCY OF ADMINISTRATION, AND LIMITED SUPPLY, THIS DRUG POSES SIGNIFICANT LOGISTICAL CHALLENGES FOR LARGE SCALE USE IN COMPARISON TO OTHER AMINOGLYCOSIDES (SPECIFICALLY GENTAMICIN). THE BOARD RECOMMENDS THE SELECTION OF THIS DRUG FOR TREATMENT WITH CIPROFLOXACIN AS A THERAPEUTIC ALTERNATIVE. FOR Q FEVER AND BRUCELLOSIS THE THERAPEUTIC CHOICE IS DOXYCYCLINE (WITH RIFAMPICIN ADDED FOR BRUCELLOSIS) WHILE FOR GLANDERS THERAPY WOULD INCLUDE CEFTAZIDIME AND RIMETHOPRIM/ SULFAMETHOXAZOLE. SPECIFIC RECOMMENDATIONS ARE INCLUDED IN THE ATTACHED TABLE.**

d. **IT IS OUR UNDERSTANDING THAT THE MANUFACTURERS OF CIPROFLOXACIN ARE ENGAGED IN DISCUSSIONS WITH FDA TO DETERMINE THE REQUIREMENTS FOR CHANGING THE LABELING TO INCLUDE PROPHYLACTIC USE AGAINST THE MAJOR BIOWARFARE THREAT AGENTS. SHOULD A LABEL CHANGE OCCUR, IT WOULD BE AN ADDED INCENTIVE TO SELECT THIS DRUG OVER DOXYCYCLINE TO BECAUSE OF THE OFF-LABEL USE ISSUE. OF NOTE, NEWER FLUOROQUINOLONES HAVE THE ADVANTAGE OF ONCE DAILY ADMINISTRATION. ALTHOUGH DOSING FREQUENCY IS MORE OF AN ISSUE IN CIVILIAN SETTINGS, THE ADDED EASE OF ADMINISTRATION WOULD BE A STRONG CONSIDERATION FOR SELECTION OF ONE OF THESE AGENTS (I.E. LEVOFLOXACIN) IF BIOEQUIVALENCY AGAINST THE THREAT AGENTS COULD BE DETERMINED AND THE COST WAS NOT SIGNIFICANTLY DIFFERENT.**

AFEB (15-1a) 00-9 03 August 2000
SUBJECT: Antibiotics Against Biowarfare Agents

e. **SPECIFIC RECOMMENDATIONS*:**

	POST-EXPOSURE PROPHYLAXIS		THERAPY	
Threat Agent	**1st Choice**	**2nd Choice**	**1st Choice**	**2nd Choice**
Anthrax	**Ciprofloxacin**	**Doxycycline**	**Ciprofloxacin**	**Doxycycline**
Plague	**Doxycycline**	**Ciprofloxacin**	**Gentamicin**	**Ciprofloxacin**
Tularemia	**Ciprofloxacin**	**Doxycycline**	**Gentamicin**	**Ciprofloxacin**
Glanders	**Doxycycline**		**Ceftazidime TMP/Sulfa**	
Brucellosis	**Doxycycline Rifampicin**		**Doxycycline Rifampicin**	
Q fever	**Doxycycline**		**Doxycycline**	

***Dosage and duration as per MBDM guidance**

6. The above comments and recommendations were unanimously approved by the Board.

7. The above comments and recommendations have been reviewed by the appropriate representatives from the CDC who also concur.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

F. MARC LAFORCE, M.D.
AFEB President

BENEDICT M. DINIEGA
Colonel, USA, MC
AFEB Executive Secretary

2 Encls
1. Question to Board
2. MBDM Recommendations

AFEB (15-1a) 00-9 03 August 2000
SUBJECT: Antibiotics Against Biowarfare Agents

Copies Furnished:
Board Members
DASG-ZH
OASD(HA)/HOP, Prog. Dir.,
Prev. Med. & Surveillance
AFMOS/SGOP
DASG-HS-PM
HQ, USMC, PMO,CAPT Kenneth W. Schor
Dep. Dir. Occup. Hlth. & Prev. Med. Div, BUMED-DN
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CDR, USACHPPM, ATTN: MCHB-DC-C
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Lcol Maureen Fensom, CFMS

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1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

MAR 13 2000

MEMORANDUM FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD

SUBJECT: Antibiotics Against Biowarfare Agents

The Armed Forces Epidemiological Board (AFEB) has been very helpful in the review and prioritization of biological threat agents facing our Armed Forces. In our continuing efforts to ensure that the most effective medical therapies are readily available for the military, we additionally require a review of antimicrobial drugs.

In light of the need for the Department of Defense to maintain a high level of readiness and to maintain adequate stockpiles of specific antibiotics, I request that the Armed Forces Epidemiological Board conduct a review of antibiotics approved by the Food and Drug Administration that may prove useful against certain infectious biological warfare agents. This review should involve appropriate consultation with Centers for Disease Control and Prevention (CDC) staff, as they will have very similar concerns regarding what is needed for the domestically-oriented national pharmaceutical stockpile for medical response to terrorism.

I ask the AFEB to provide recommendations to this office on the most appropriate antibiotics that would be indicated for the treatment of the primary bacterial and rickettsial agents on the biowarfare threat list. Of greatest concerns are the infectious agents causing anthrax, plague, tularemia, brucellosis, glanders, and Q fever. The recommendations should describe any precautions or contraindications associated with the administration of any antibiotics.

I request that you address this issue at your next AFEB meeting in May in concert with your periodic review of the threat list and provide your results within 60 days of your meeting.

J. Jarrett Clinton

RADM J. Jarrett Clinton, MD, MPH, USPHS
Deputy Assistant Secretary of Defense
(Health Operations Policy)

Medical Biological Defense Material (MBDM) Policy Meeting
1000-1200, 01 DEC 99
USAMRIID
Fort Detrick, MD

1. Attendees: See Annex A

2. Introductory Comments:

- Antibiotics have already been fielded for use as post exposure prophylaxis against Biological Warfare (BW) agents (i.e. Desert Shield, Desert Storm, Desert Thunder).
- Antibiotics are expensive, but the Army has shown their willingness to support this cost. OTSG has programmed $4M into the FY02-05 POM in support of Force Packages 1 & 2 and Forward Deployed (370,000 personnel).
- Issuing antibiotics to Servicemembers for use as post exposure prophylaxis for BW agents is generally interpreted as an "Off Label" Use – not FDA approved and thus a complex and sensitive legal issue. MMWR (Feb 99) is not FDA Policy. "Off Label" doe not equate "Inappropriate" but ASD(HA) will not currently promulgate Policy promoting "Off Label" use.

At the Service level, we do write policy and doctrine: Draft FM 8-284 addresses and outlines the use of antibiotics as a prophylaxis with vaccine as a treatment.

We discussed the potential for abuse but it is regarded as negligible in the face of a BW threat.

After defining and reviewing ANNEX B, Doxy and Cipro were the recommended contenders for use as the primary drug.

Issues:

- Taking Doxy and Cipro simultaneously increases side effects.
- Doxy may have more severe side effects (photosynthesis and GI tract upset) than Cipro.
- With 2 of 3 of the lethal BW agents, use of Cipro is advantageous over Doxy.
- Cipro may work well enough on remainder agents.
- If anthrax is major concern – Cipro is preferred with a theater reserve of Doxy.

If we recommend one drug, access to second drug must be available – we will have to maintain a contingency stockpile within the medical system, at the very least. The contingency drug stockpile is maintained to address the issue of Servicemembers who do not respond to the primary drug prophylaxis – who, for one reason or another, become ill from exposure to either the primary prophylactic antibiotic or the BW agent. This drug would be stockpiled within the medical system to allow for administration on a physician's advice.

There is no label recommendation for prophylaxis of these agents. There is little or no animal or human data for the use of any drug for prophylaxis.

Currently, only Chemical Casualty Treatment Sets are fielded. Maintenance of these sets is the responsibility of the individual units, with some supplemental support from OTSG. There is a proposal circulating within the logistics community for the Potency & Dated (Ps &Ds) in the Chemical Casualty Treatment Sets to be centrally managed within the DRBs under MDEP HSCB.

AMEDDC&S, DCDD defines the doctrine which defines the type, severity, and number of casualties and the treatment necessary. Strong consideration should be given to fielding a BW agent treatment capability.

3. MEDICAL RECOMMENDATION:

Ciprofloxacin is recommended as the primary drug
2 tabs / day X 30 days X 370K Servicemembers
Doxycyline is recommended as a contingency backup
2 tabs / day X 30 days X 370K Servicemembers X 25% (Contingency Factor)

4. Logistical Supportability:

Cipro

Per Bayer, the current FSS price for Ciprofloxacin is $179.96 for the individually sealed product.

tabs/day	days	# soldiers		total tablets
2	30	370,314		22,218,840
# packages of 100 required:				222,188
7-year shelf life; buy 1/7 ea. yr:				31,741
Price per package(w/ addition of PV CRR (1.3%)			$	182.30
Total cost per year (constant 00)			$	**5,786,420.76**

Doxy

The Prime Vendor price for Doxycycline, 100mg, 100s Individually Sealed is $9.30 (WRAMC PV cost).

tabs/day	days	# soldiers		total tablets
2	30	370,314		22,218,840
Contingency - need 25%				5,554,710
# packages of 100 required:				55,547
2-year shelf life; buy 1/2 ea. yr:				27,774
Price per package: (w/ addition of PV CCR (1.3%)			$	9.42
Total cost per year (constant 00)			$	**261,626.84**

The surge capacity is relatively robust for either Doxy or Cipro but greater for Doxy.

5. Follow-on Actions:

a. LTC Scott, DCDD, will introduce this issue to MPSP on 7 Dec 99 for Principal Signature in Feb 00.

b. LtCol Christopher, USAMRIID, will draft the detailed technical medical analysis (ANNEX B) for recommendations to decide which drug will be used as prophylaxis for post exposure to BW agents. A preliminary report will be prepared for DCDD for the MPSP meeting 7 Dec 99.

c. USAMMA will provide an estimate of storage, shelf life extension, maintenance/sustainment etc. (i.e. an analysis of the total logistical sustainability of this proposal).

d. Issues regarding the definition of "Credible Evidence" of exposure will be addressed separately:

- What is the accepted hierarchy of information?
- How do we define the criteria for administration of a post exposure prophylactic?
- What is a "credible exposure?"
- Is there precedent in this from PB?

ANNEX A

NAME	*ORGANIZATION*	*PHONE*	*EMAIL*
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Medical Biological Defense Material (MBDM) Policy Meeting
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ANNEX B

Best Medical Advice: (only addressing post exposure prophylaxis, not in personnel)

AGENT	ANTIBIOTIC	ROUTE	TIME	COMMENTS
Anthrax	#1 - Ciprofloxacin	500mg po bid	30 days	adjunct to vaccination
	#2 - Doxycycline	100mg po bid		doxy resistant strains Also Considered: Penicillin, tetracycline Off label for both drugs
Plague	#1 – Doxycycline	100mg po bid	1 wk	off label, is for therapy (recommended by CDC)
	#2 – Cipro	500mg po bid	1 wk	off label Also considered: Tetracycline, Chloramphenicol
Tularemia	#2 – Doxy	100mg po bid	2 wk	relapses w/ Doxy treatment
	#3 – Tetra #1 – Cipro	500mg	4 wk	off label
Glanders/ Melioidosis	#1 – Doxy TMP-SMX	100mg po bid treatment recommendations only Combination therapy – for acute sepsis	2 wk	in vitro, off label
Brucellosis	#1 – Doxy	200mg po /day	6 wk	full course of therapy advised
	#1 – Rifampin #2 - Ofloxacin	600-900 mg po /day		combined therapy
Q Fever	#1 – Doxy	100mg po bid	5 days beginning day 8 through 12	
	Tetracycline considered (based on treatment)	500mg po bid	5 days,8-12 days post exposure	
Cholera	recommended not considering this agent for chemoprophylaxis			